DETAILED ACTION

1. Claims 2, 3, 10, 11, 14, 21, 23, 24, 29-128, 130-134 and 143 have been cancelled. Claims 147-166 are new.

Newly submitted claims 147-166 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the new claims 147-166 are drawn to new independent and distinct immunization protocols, and thus introduce new limitations that require a distinct search from the search required for the originally presented invention.

It is noted that the applicant argues that claims 147-166 read on the elected invention. This argument is not new and was previously addressed.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 147-166 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142 and 144-146 are under examination.

Response to Arguments

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as

to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1, 5-9, 12, 15-18, 22, 129, 135-137, 139-142 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 5, 9-11, and 13 of the presently allowed Application No. 10/300,247. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The instant claims are drawn to a method of inducing a mucosal immune response by administering to a subject an oligonucleotide 8 to 100 nucleotides long and a viral antigen not encoded by a nucleic acid; the oligonucleotide has the formula 5' $X_1X_2CGX_3X_4$ 3', wherein C is unmethylated, X_1, X_2, X_3, and X_4 are nucleotides, and both the oligonucleotide and the antigen are administered intranasally or ocularly (claims 1, 22, 129, 135-137, and 139-142). The antigen is delivered in colloidal dispersion

systems (claims 5-7), the method further comprises administering a non-oligonucleotide adjuvant, such as MPL (claims 8 and 9), the subject is at risk of developing an infectious disease (claim 12), the oligonucleotide contains phosphorothioate modifications at the 5' end or the 3' end (claims 15-17), X_1X_2 could be GpT and X_3X_4 could be TpT (claim 18). The specification defines that the viral antigen could be a hepatitis B viral antigen and therefore, the vaccine could be used to elicit an immune response in a subject infected with hepatitis B therefore, i.e., the vaccine can be used to treat a subject infected with hepatitis B (p. 27, lines 14-23, p. 29, line 14, p. 40, lines 13 and 14).

The application claims recite a method of treating a subject infected with hepatitis via inducing an immune response against hepatitis virus by administering to the subject an oligonucleotide 8 to 100 nucleotides long, an antigen, and a non-nucleic acid adjuvant (claims 1, 4, and 12), wherein the non-nucleic acid adjuvant could be MPL (claim 5); the oligonucleotide has the formula 5' $X_1X_2CGX_3X_4$ 3' wherein C is unmethylated, X_1, X_2, X_3, and X_4 are nucleotides, and the oligonucleotide contains phosphorothioate modifications at the 5' end or the 3' end (claims 9-11 and 13). The specification defines that the antigen could be a polypeptide (i.e., not encoded by a nucleic acid vector), the non-nucleic acid adjuvant could be a liposome (i.e., micellar, lipid-based system), and that the delivery could be intranasal or ocular (p. 3, lines 11 and 12, p. 16, lines 5-13, p. 27, lines 16 and 17). Although the application claims do not recite a mucosal immune response, such is inherent to the application method. This is because the oligonucleotide recited in the application claims is identical to the instant

oligonucleotide and therefore, its intranasal or ocular delivery necessarily results in a mucosal immune response.

Since the application claims embrace all the limitations of the instant claims, the application claims and the instant claims are obvious variants.

Applicant states that the rebuttal of the provisional double patenting rejection is deferred until the cited co-pending application is allowed.

Applicant's statement is acknowledged; however, the claims of the copending application were allowed, and thus the rejection will be maintained until a terminal disclaimer is filed or the instant claims are amended to obviate the rejection.

4. Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142 and 144-146 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-22 of the U.S. Patent No. 7,488,490 (filed as Application No. 10/023,909), in view of Craig (U.S. Patent No. 6,689,757). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The claims are obvious variants because both claim sets encompass a method of inducing mucosal immune response via administering to a subject a composition comprising an antigen, an oligonucleotide having the formula 5' $X_1X_2CGX_3X_4$ 3', wherein C is unmethylated and X_1, X_2, X_3, and X_4 are nucleotides, and a non-oligonucleotide adjuvant such as MPL. The patent specification defines that delivery

could be intranasal, rectal or vaginal (see column 32, lines 47-50). Although the patent claims do not specifically recite a mucosal immune response, such is inherent to the application method. This is because the oligonucleotide recited in the patent claims is identical to the instant oligonucleotide and therefore, its intranasal, rectal, or vaginal delivery necessarily results in a mucosal immune response. The patent claims do not recite further using B-7, as recited in the instant claim 25. Craig teaches using B-7 to upregulate the immune response to vaccines (column 6, lines 35-49). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the patent claims by further using B-7 costimulatory molecule, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to enhance the immune response elicited against the vaccine of interest. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that B-7 can be successfully used to potentate the immune responses to antigens.

Thus, the instant claims and the patent claims are obvious variants.

Most of the arguments are not new and were previously addressed.

The applicant argues that the patent claims do not recite mucosal administration. This is not found persuasive because the patent specification defines that administration could be intranasal, rectal or vaginal, i.e., the patent claims encompass mucosal administration, which would necessarily result in a mucosal immune response.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142, and 144-146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (U.S. Patent No. 6,239,116) in view of each Agrawal et al. (U.S. Patent No. 6,426,334), Briles et al. (U.S. Patent No. 6,042,838), Craig (U.S. Patent No. 6,689,757), and Kincy-Cain et al. (Infection and Immunity, 1996, 64: 1437-1440).

Krieg et al. teach a method of inducing an immune response in a subject by orally administering to the subject an oligonucleotide 8 to 100 nucleotides in length, wherein the oligonucleotide can be administered by itself or concurrently with an antigen; the oligonucleotide has a sequence which includes the formula 5' $X_1X_2CGX_3X_4$ 3' wherein C is unmethylated, X_1, X_2, X_3, and X_4 are nucleotides, the oligonucleotide contains phosphorothioate modifications at the 5' end or the 3' end, X_1X_2 could be GpT, and X_3X_4 could be TpT (claims 1, 4, 15-18, 136-139, and 141) (Abstract, column 6, lines 1-67, column 7, column 14, lines 3-32, column 28, lines 4-25, column 45, lines 36-42, column 46, lines 55-60). Krieg et al. teach that the administration of the oligonucleotide by itself results in an immune response; such an immune response would protect a subject from subsequent passive exposure to antigen (claim 138) (columns 6, lines 38-51). Krieg et al. teach that a non-oligonucleotide adjuvant could be included in the

immunogenic composition (claim 8), that the antigen could be a protein, i.e., not encoded by a nucleic acid vector (claims 1, 20, 136, 137, 139, 141, 142, and 144-146) (column 7, lines 1-7, column 9, lines 48-53), and that the method could be used to induce an immune response in subjects to eliminate tumors or viral infections (claims 12, 13, 135, and 140) (column 10, lines 23-61). Krieg et al. teach administering the composition in conjunction with liposomes (claims 5-8) (column 13, lines 40-45, column 45, lines 6-17). Krieg et al. teach their oligonucleotide as having the formula 5' TCCATGTCGTTCCTGTCGTT3' (SEQ ID NO: 73), i.e., comprising the sequence 5' $TCNTX_1X_2CGX_3X_4$ 3' wherein N is 2 (claim 19) (column 32, Table 10). Krieg et al. also teach boosting with oligonucleotide to enhance the immune responses to the vaccines (claim 27) (column 47, lines 10-29). The limitation of inducing a mucosal immune response is inherent to the method of Krieg et al. because all that is required to achieve such is to administer their oligonucleotide to a mucosal site. With respect to the limitation recited in claim 28, it would have been obvious to one of skill in the art to include the non-nucleic acid adjuvant in the boost in order to improve the results.

Krieg et al. do not teach specifically the recited routes of administration recited in the instant claims 1, 136, 137, 139 and 141. However, at the time of filing such administration routes were taught by the prior art. For example Agrawal et al. teach inducing an immune response by administering oligonucleotides having a sequence including the claimed formula via intranasal or rectal administration (claims 1, 136, 137, 139, and 141) (column 5, lines 30-45, column 6, lines 48-50). It would have been obvious to one of skill in the art, at the time the invention was made, to substitute the

oral administration of Krieg et al. with the intranasal or rectal administration of Agrawal et al. to achieve the predictable result of inducing immunity. The limitation of the intranasal immunization resulting in mucosal immunity at remote sites (claim 26) is an inherent feature of their method because all that is required to achieve such is to intranasally administer their oligonucleotide.

Although Krieg et al. and Agrawal et al. teach the use of non-nucleic acid adjuvants, they do not specifically teach the adjuvants recited in claim 9. However, at the time the invention was made, such adjuvants were well known and used in the prior art. For example Briles et al. teach the use of saponins or cholera toxin and its B subunit (column 4, lines 20-30, column 8, lines 14-18). It would have been obvious to one of skill in the art to use an adjuvant such as cholera toxin in the method of Krieg et al. and Agrawal et al. to achieve the predictable result of eliciting an immune response.

Krieg et al., Agrawal et al., and Briles et al. do not teach administering B-7 costimulatory molecule (claim 25). Craig teaches using B-7 to upregulate the immune response to vaccines (column 6, lines 35-49). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Krieg et al., Agrawal et al., and Briles et al. by further using B-7 costimulatory molecule, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to enhance the immune response elicited against the vaccine of interest. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that B-7 can be successfully used to potentate the immune responses to antigens.

With respect to the limitation recited in claim 129, it is noted that Krieg et al. teach their oligonucleotide as being capable of inducing IL-12 (column 6, lines 1-51, column 35, lines 50-67). The prior art teaches that IL-12 induces mucosal immune responses against intracellular pathogens and it is useful as a mucosal adjuvant for vaccines used to prevent or treat infectious with pathogens which gain entry via a mucosal surface (see Kincy-Cain et al., Abstract, p. 1437, column 1, second paragraph, p. 1439, column 2). Based on these teachings, one of skill in the art would have known that the oligonucleotide of Krieg et al. is a mucosal adjuvant which could be used to treat subjects in need of mucosal immunization.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

The arguments are not new and were previously addressed.

The applicant argues that the instant claims are not obvious because, prior to the instant invention, it was not known or reasonably expected that CpG oligonucleotides could induce mucosal immunity. This is not found persuasive. As set forth in the rejection above, Krieg et al. teach their CpG as being capable of inducing IL-12 and Kincy-Cain et al. teach that IL-12 induces mucosal immune responses against intracellular pathogens and it is useful as a mucosal adjuvant for vaccines used to prevent or treat infectious with pathogens which gain entry via a mucosal surface. Thus, prior to the instant invention, it was known or reasonably expected that CpG oligonucleotides would induce mucosal immunity. Furthermore, the prior art teaches

that oral administration of antigen (as taught by Krieg et al.) results in mucosal immunity (Bergmann et al., Rev. Infect. Dis., 1988, 10: 939-950, see Abstract). Based on the teachings in the prior art as a whole, one of skill in the art would have known that Krieg et al. teach inducing a mucosal immune response.

Conclusion

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Bergmann et al. (Rev. Infect. Dis., 1988, 10: 939-950, Abstract) was cited to evidence that the oral administration taught by the cited prior art results in a mucosal immune response.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633